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(21) International Application Number: PCT/GB91/01887 (22) International Filing Date: 29 October 1991 (29.10.91) (30) Priority data: 9023498.0 29 October 1990 (29.10.90) GB (71) Applicant (for all designated States except US): BIOCOMPATIBLES LIMITED [GB/GB]; Brunel Science Parc, Kingston Lane, Uxbridge UB8 3PQ (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : BOWERS, Roderick, William, Jonathon [GB/GB]; STRATFORD, Peter, William [GB/GB]; JONES, Stephen, Alistair [GB/GB]; Biocompatibles Limited, Brunel Science Park, Kingston Lane, Uxbridge UB8 3PQ (GB).		(74) Agents: CRESSWELL, Thomas, Anthony et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU (GB). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: CONTACT LENS MATERIAL (57) Abstract Cross-linked copolymers which are obtainable by polymerising a neutral diluent monomer or monomers, a monomer or monomers bearing a centre of permanent positive charge, and a bifunctional and/or trifunctional cross-linking agent, are suitable for use in contact lenses. Process for producing them by copolymerisation, contact lens material comprising them, contact lenses made of them and processes for producing contact lenses from them.		

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CONTACT LENS MATERIAL

The present invention relates to copolymers, in particular suitable for use in contact lenses.

The use of synthetic hydrogels for contact lenses was
5 first demonstrated by Wichtecte and Lim in the 1960's.

Early hydrogels employed 2-hydroxyethyl methacrylate (HEMA) as principal monomer, together with some of the homologous esters of the glycol monomethacrylate series such as diethylene glycol monomethacrylate and tetraethylene glycol
10 monomethacrylate. It was later found that slightly cross-linked copolymers of the higher glycol monomethacrylates and 2-hydroxyethyl methacrylate yielded transparent hydrogels that swelled in water to a higher hydration than the hydrogels of 2-hydroxyethyl methacrylate.

15 The water content of hydroxyalkyl methacrylate based gels can be further increased by the addition of vinyl lactams, methacrylic acids, acrylic acids, acrylamides and methacrylamides. Although the required degree of gel hydration can be achieved by the addition of anionic
20 monomers, it is well known that these gels display high levels of protein deposition on and occasionally within the gel matrix.

It has now surprisingly been found that effective contact lens materials which have both good transparency
25 and a high degree of water swellability are provided by copolymers which have a permanent positive charge built

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into them. Such polymers are formed by polymerising and crosslinking a neutral diluent monomer, for example HEMA, with a co-monomer bearing a centre of permanent positive charge. These formulations have been found to have a high
5 level of protein resistance to tear component deposition and a reduction in lens water loss.

Accordingly, the present invention provides a crosslinked copolymer which is obtainable by polymerising a neutral diluent monomer or monomers, a monomer or monomers
10 bearing a centre of permanent positive charge, and a bifunctional or trifunctional crosslinking agent.

The crosslinked copolymers of the present invention therefore comprise residues of a diluent monomer or monomers, a monomer or monomers bearing a centre of
15 permanent positive charge, and a bifunctional or trifunctional crosslinking agent.

The copolymers of the invention may be xerogels which do not contain any water. Alternatively, they may be in the form of hydrogels which do contain water.

20 The invention also provides a process for producing such a crosslinked copolymer, a contact lens material comprising such a copolymer, a contact lens made from such a copolymer, and use of such a copolymer or contact lens material in the production of a contact lens.

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Diluent Comonomer

The diluent monomer can act as a solvent for the comonomers during copolymerisation to produce the copolymer if no additional solvent is present. Where the diluent monomer and monomer bearing the centre of permanent positive charges are immiscible a solvent can be used to aid mixing.

Particular examples of diluent comonomers include alkyl (alk)acrylate preferably containing 1 to 12, more preferably 1 to 4, carbon atoms in the alkyl group of the ester moiety, such as a methyl (alk)acrylate and butyl (alk)acrylate; a dialkylamino alkyl (alk)acrylate, preferably containing 1 to 4 carbon atoms in each alkyl moiety of the amine and 1 to 4 carbon atoms in the alkylene chain, e.g. 2(dimethylamino)ethyl (alk)acrylate; an alkyl (alk)acrylamide preferably containing 1 to 4 carbon atoms in the alkyl group of the amide moiety; a hydroxyalkyl (alk)acrylate preferably containing from 1 to 4 carbon atoms in the hydroxy moiety, e.g. a 2-hydroxyethyl (alk)acrylate; or a vinyl monomer such as an N-vinyl lactam, preferably containing from 5 to 7 atoms in the lactam ring for instance vinyl pyrrolidone; styrene or a styrene derivative which for example is substituted on the phenyl ring by one or more alkyl groups containing from 1 to 4 carbon atoms, and/or by one or more halogen, such as fluorine atoms.

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It is to be understood that throughout the specification (alk)acrylate, (alk)acrylic and (alk)acrylamide mean acrylate or alkacrylate, acrylic or alkacrylic and acrylamide or alkacrylamide respectively. Preferably

5 alkacrylate, alkacrylic and alkacrylamide groups contain from 1 to 4 carbon atoms in the alkyl group thereof and are most preferably methacrylate, methacrylic or methacrylamide groups. Similarly (meth)acrylate, (meth)acrylic and (meth)acrylamide shall be understood to mean acrylate or

10 methacrylate, acrylic or methacrylic and acrylamide or methacrylamide respectively.

Preferably the diluent monomer is selected from vinylpyrrolidone, 2-hydroxyethyl methacrylate, methyl methacrylate and mixtures thereof, most preferably 2-

15 hydroxyethyl methacrylate, methyl methacrylate and mixtures thereof. In one embodiment diluent monomers are vinylpyrrolidone, 2-hydroxyethyl methacrylate and mixtures thereof.

Comonomers Bearing A Centre of Permanent Positive Charge.

20 The comonomer bearing the centre of permanent positive charge can either be cationic or zwitterionic. In the latter case the monomer includes within its structure not only a centre of permanent positive charge but also a centre of negative charge. Typically the centre of

25 permanent positive charge in both cationic and zwitterionic comonomers is provided by a quaternary nitrogen atom.

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Preferred comonomers which bear a centre of positive charge are of general formula (I)

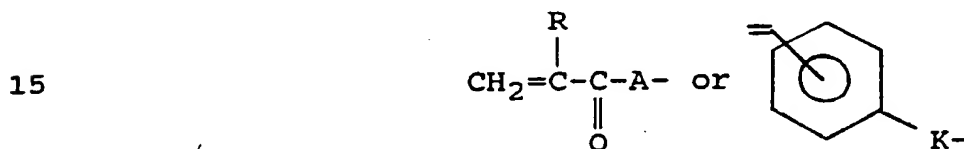


wherein B is a straight or branched

5 alkylene, oxaalkylene or oligo-oxaalkylene chain or if X contains a carbon-carbon chain between B and the centre of permanent positive charge or if Y contains a terminal carbon atom, a valence bond,

X is a group bearing a centre of permanent positive
10 charge and

Y is an ethylenically unsaturated polymerisable group selected from



wherein:

20 R is hydrogen or a C₁-C₄ alkyl group;

A is -O- or -NR¹- where R¹ is hydrogen or a C₁-C₄ alkyl group or R¹ is -B-X where B and X are as defined above.

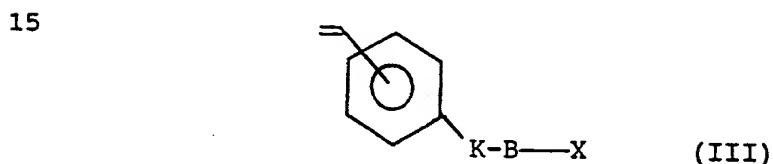
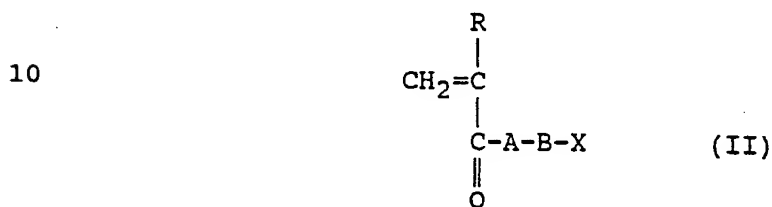
K is a group -(CH₂)_pOC(O)-, -(CH₂)_pC(O)O-,
 -(CH₂)_pOC(O)O-, -(CH₂)_pNR²-, -(CH₂)_pNR²C(O)-,
 25 -(CH₂)_pC(O)NR²-, (CH₂)_pNR²C(O)O-, -(CH₂)_pOC(O)NR²-,
 -(CH₂)_pNR²C(O)NR²- (in which the groups R² are the same or different), -(CH₂)_pO-, -(CH₂)_pSO₃-, or, optionally in a combination with B, a valence bond, and p is from 1 to 12

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and R^2 is hydrogen or a C_1 - C_4 alkyl group.

The proviso on whether B may be a valence bond ensures that the centre of permanent positive charge in X is not directly bonded to a heteroatom, such as an oxygen or
 5 nitrogen atom in Y.

Preferred monomers which bear a centre of positive charge are those of general formula (II) or (III).



where R, A, B and X are as defined with reference to
 20 formula (I).

Preferably R is hydrogen, methyl, or ethyl, more preferably methyl, so that the monomer of formula (II) is an acrylic acid, methacrylic acid or ethacrylic acid derivative.

25 In the compounds of formula (III) K may be a valence bond and B a group, K may be a group and B a valence bond, both K and B may be groups or K and B may together be a valence bond. Preferably B is a group where K is a valence bond. Where K is a group then preferably p is from 1 to 6,
 30 more preferably 1, 2 or 3 and most preferably p is 1. When

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K is a group $-(CH_2)_pNR^2-$, $-(CH_2)_pNR^2C(O)-$, $-(CH_2)_pC(O)NR^2-$, $-(CH_2)_pNR^2C(O)O-$, $-(CH_2)_pOCNR^2-$ or $-(CH_2)_pNR^2C(O)NR^2-$ then R^2 is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

5 Preferably B is:

an alkylene group of formula $-(CR^3_2)_a-$, wherein the groups $-(CR^3_2)-$ are the same or different, and in each group $-(CR^3_2)-$ the groups R^3 are the same or different and each group R^3 is hydrogen or C_{1-4} alkyl, preferably

10 hydrogen, and a is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$;

an oligo-oxaalkylene group of formula
 15 $-[(CR^4_2)_bO]_c(CR^4_2)_b-$ where the groups $-(CR^4_2)-$ are the same or different and in each group $-(CR^4_2)-$ the groups R^4 are the same or different and each group R^4 is hydrogen or C_{1-4} alkyl, preferably hydrogen, and b is 2 or 3 and c is from 2 to 11, preferably 2 to 5;

20 or a valence bond but only if X contains a carbon-carbon chain between B and the centre of positive charge, or if Y contains a terminal carbon atom.

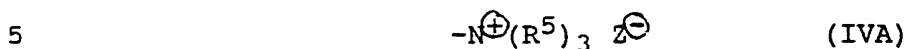
Preferred groups B include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon
 25 atoms.

Preferred groups X are the groups of formula (IVA),

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(IVB), (IVC), (IVD), (IVE) and (IVF) as defined below, of which the groups of formula (IVC) are particularly preferred.

The groups of formula (IVA) are:



where the groups R^5 are the same or different and each is hydrogen or C_{1-4} alkyl and Z^{\ominus} is a counterion.

Preferably the groups R^5 are all the same. It is also preferable that at least one of the groups R^5 is methyl, and more preferable that all the groups R^5 are methyl.

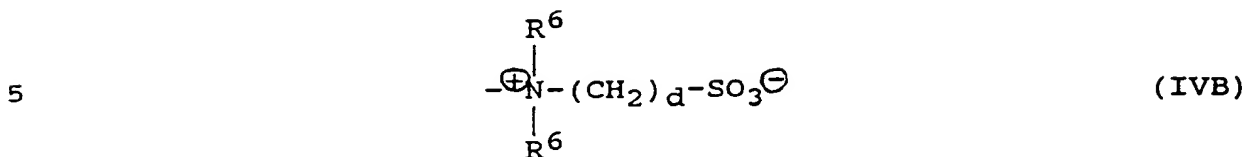
The counterion Z^{\ominus} present in the compounds of formula (II) or (III) containing a group of formula (IVA) is such that the compounds are neutral salts. The counterion may be exchanged with ions in physiological fluids and thus the specific nature of the counterion is not critical in the present invention. However, physiologically acceptable counterions are preferred. Suitable physiologically acceptable counterions include halide anions, such as chloride, bromide or fluoride ions, other inorganic anions such as sulphate, phosphate and phosphite and organic anions such as aliphatic mono-, di- or tri-carboxylate anions containing from 2 to 25 carbon atoms and optionally bearing one or more hydroxyl groups e.g. acetate, citrate and lactate.

When X is a group of formula (IVA), preferably B is a group of formula $-(CR^3_2)-$ or $-(CR^3_2)_2-$, eg. $-(CH_2)-$ or

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-(CH₂CH₂)-.

The groups of formula (IVB) are:



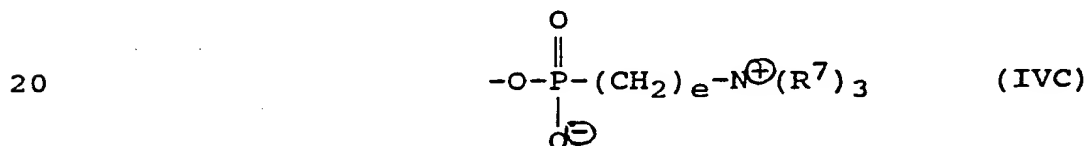
where the groups R⁶ are the same or different and each is hydrogen or C₁₋₄ alkyl and d is from 2 to 4.

10 Preferably the groups R⁶ are the same. It is also preferable that at least one of the groups R⁶ is methyl, and more preferable that the groups R⁶ are both methyl.

Preferably d is 2 or 3, more preferably 3.

When X is a group of formula (IVB) preferably B is a
15 group of formula -(CR³₂)- or -(CR³₂)₂-,
eg. -(CH₂)- or -(CH₂CH₂)-.

The groups of formula (IVC) are:



where the groups R⁷ are the same or different and each is hydrogen or C₁₋₄ alkyl, and e is from 1 to 4.

25 Preferably the groups R⁷ are the same. It is also preferable that at least one of the groups R⁷ is methyl, and more preferable that the groups R⁷ are all methyl.

Preferably e is 2 or 3, more preferably 2.

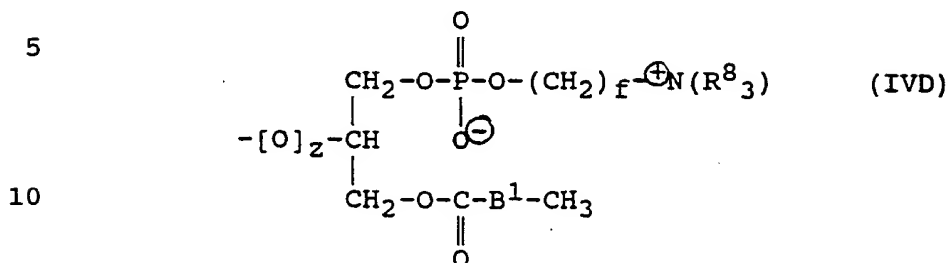
When X is a group of formula (IVC) preferably B is a

- 10 -

group of formula $-(CR^3_2)-$ or $-(CR^3_2)_2-$,

eg. $-(CH_2)-$ or $-(CH_2CH_2)-$.

The groups of formula (IVD) are:



wherein the groups R^8 are the same or different and each is
 15 hydrogen or C_{1-4} alkyl, B^1 is a valence bond or straight or
 branched alkylene, oxaalkylene or oligo-oxaalkalkylene
 group, f is from 1 to 4 and if B is other than a valence
 bond, Z is 1 and if B is a valence bond Z is 0 if X is
 directly bonded to an oxygen or nitrogen atom, and
 20 otherwise Z is 1.

Preferably the groups R^8 are the same. It is also
 preferable that at least one of the groups R^8 is methyl,
 and more preferable that the groups R^8 are all methyl.

Preferably f is 1 or 2, more preferably 2.

25 Preferably B^1 is:

a valence bond;

an alkylene group of formula $-(CR^{3a}_2)_{aa}-$, wherein the
 groups $-(CR^{3a}_2)-$ are the same or different, and in each
 group $-(CR^{3a}_2)-$ the groups R^{3a} are the same or different
 30 and each group R^{3a} is hydrogen or C_{1-4} alkyl, preferably
 hydrogen, and aa is from 1 to 24, preferably 6 to 18;

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an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably

$-\text{CH}_2\text{O}(\text{CH}_2)_4-$; or

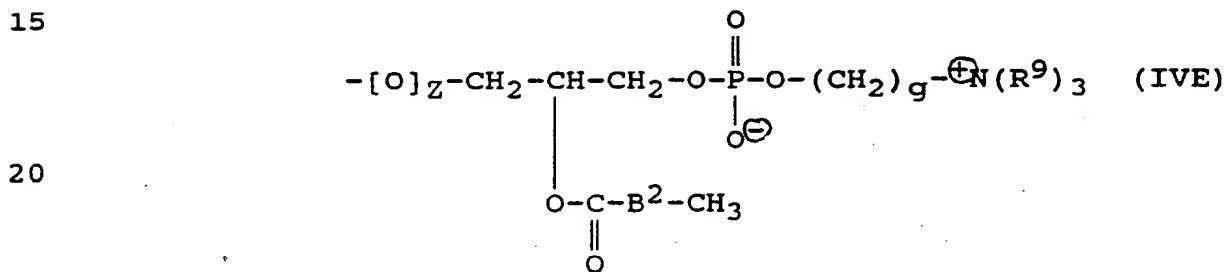
an oligo-oxaalkylene group of formula

5 $-\text{[(CR}^{4a}_2\text{)}_{ba}\text{O}]_{ca}-$ where the groups $-(\text{CR}^{4a}_2)-$ are the same or different and in each group $-(\text{CR}^{4a}_2)-$ the groups R^{4a} are the same or different and each group R^{4a} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ba is 2 or 3 and ca is from 1 to 12, preferably 1 to 6.

10 Preferred groups B^1 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 24 carbon atoms.

In one embodiment B and B^1 are the same.

The groups of formula (IVE) are:



wherein the groups R^9 are the same or different and each is
 25 hydrogen or C_{1-4} alkyl, B^2 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, g is from 1 to 4 and if B is other than a valence bond, Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise
 30 Z is 1.

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Preferably the groups R^9 are the same. It is also preferable that at least one of the groups R^8 is methyl, and more preferable that the groups R^8 are all methyl.

Preferably g is 1 or 2, more preferably 2.

5 Preferably B^2 is:

a valence bond;

an alkylene group of formula $-(CR^{3b}_2)_{ab}-$, wherein the groups $-(CR^{3b}_2)-$ are the same or different, and in each group $-(CR^{3b}_2)-$ the groups R^{3b} are the same or different
10 and each group R^{3b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ab is from 1 to 24, preferably 6 to 18;

an oxaalkylene group such as alkoxyalkyl having 1 to 6, carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

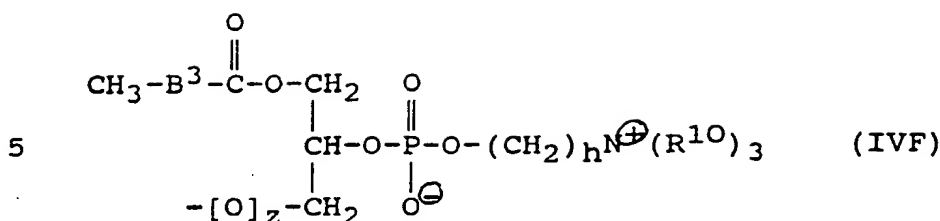
15 an oligo-oxaalkylene group of formula $-[(CR^{4b}_2)_{bb}O]_{cb}-$ where the groups $-(CR^{4b}_2)-$ are the same or different and in each group $-(CR^{4b}_2)-$ the groups R^{4b} are the same or different and each group R^{4b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bb is 2 to 6 and cb is
20 from 1 to 12, preferably 1 to 6.

Preferred groups B^2 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 24 carbon atoms.

In one embodiment B and B^2 are the same.

25 The groups of formula (IVF) are:

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wherein the groups R^{10} are the same or different and each is hydrogen or C_{1-4} alkyl, B^3 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, h is from 1 to 4 if B is other than a valence bond, Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1.

15 Preferably the groups R^{10} are the same. It is also preferable that at least one of the groups R^{10} is methyl, and more preferable that the groups R^{10} are all methyl.

Preferably h is 1 or 2, more preferably 2.

Preferably B^3 is:

20 a valence bond;

an alkylene group of formula $-(\text{CR}^{3\text{C}}_2)_{\text{ac}}-$, wherein the groups $-(\text{CR}^{3\text{C}}_2)-$ are the same or different, and in each group $-(\text{CR}^{3\text{C}}_2)-$ the groups $\text{R}^{3\text{C}}$ are the same or different and each group $\text{R}^{3\text{C}}$ is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ac is from 1 to 24, preferably 6 to 18;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-\text{CH}_2\text{O}(\text{CH}_2)_4-$; or

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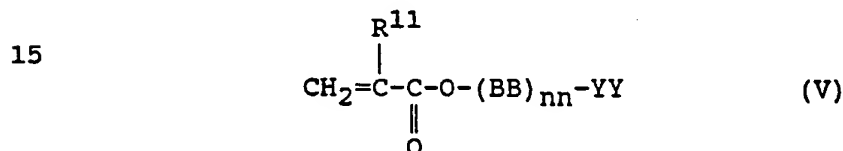
an oligo-oxaalkylene group of formula

5 $-\left[(\text{CR}^4\text{C}_2)_{bc}\text{O}\right]_{cc}-$ where the groups $-(\text{CR}^4\text{C}_2)-$ are the same or different and in each group $-(\text{CR}^4\text{C}_2)-$ the groups R^4C are the same or different and each group R^4C is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bc is 2 to 6 and cc is from 1 to 12, preferably 1 to 6.

Preferred groups B^3 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 24 carbon atoms.

10 In one embodiment B and B^3 are the same.

According to one particular embodiment, the monomer bearing a centre of permanent positive charge is a monomer of formula (V)



wherein BB is a straight or branched $\text{C}_1\text{-C}_6$ alkylene chain
20 optionally interrupted by one or more oxygen atoms;

nn is from 1 to 12

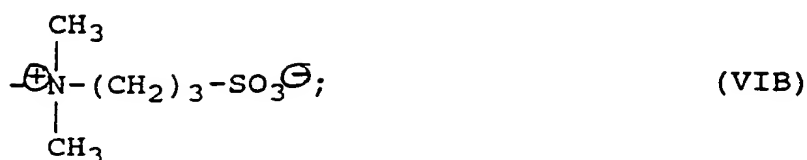
R^{11} is H or a $\text{C}_1\text{-C}_4$ alkyl group; and

YY is a group which includes a centre of positive charge. More preferably,

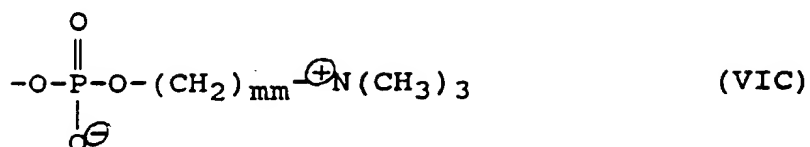
25 YY is a group selected from:



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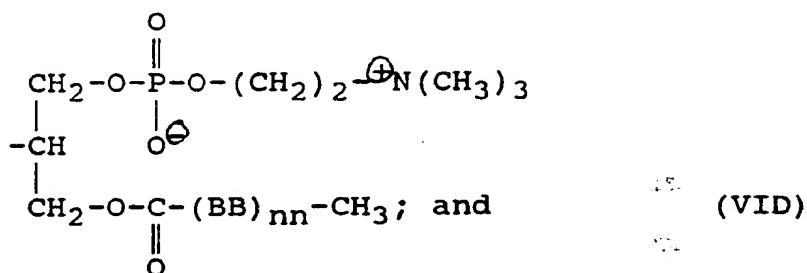


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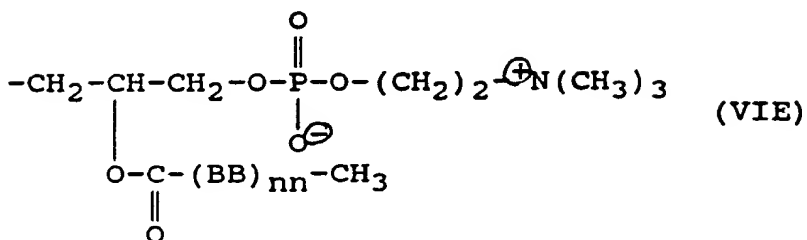
10

in which mm is from 1 to 4;



15

20



25

the group BB in (VID) and (VIE) being a linear or
30 branched alkylene chain as defined above and nn being as
defined above.

Preferably BB is a group selected from $-\text{CH}_2-$, $-\text{C}(\text{R}^{12})_2-$,
in which R^{12} is C_1 - 4 alkyl, and $-\text{CH}_2-\text{CH}_2-\text{O}-$.

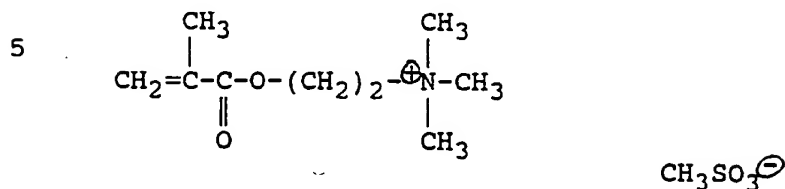
Preferably in compounds of formula (V), R^{11} is hydrogen
35 or methyl.

When X is a group as defined under (VID) or (VIE), the
group $(\text{BB})_{\text{nn}}$ is preferably chosen to avoid steric hindrance
in the vicinity of the adjacent

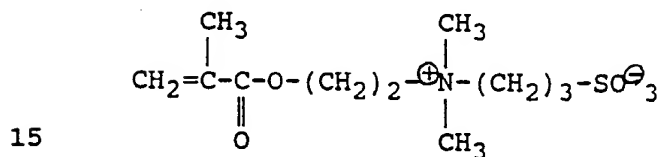
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-OC(O)- group, the reactivity of which could be adversely affected by such steric hindrance.

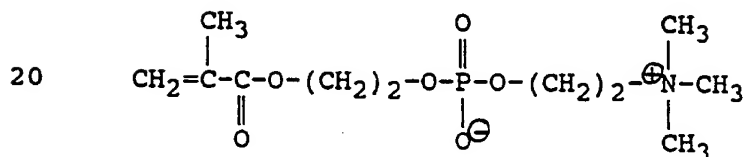
Preferred examples of co-monomers of formula (I) are:



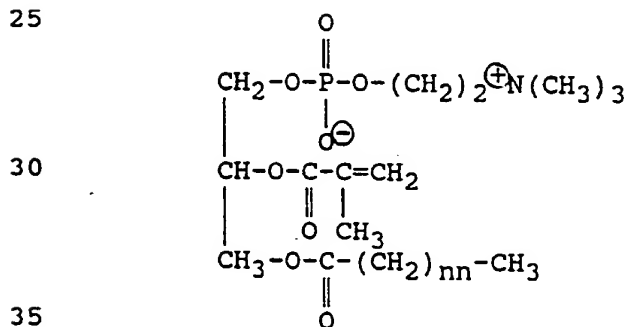
Compound A



Compound B

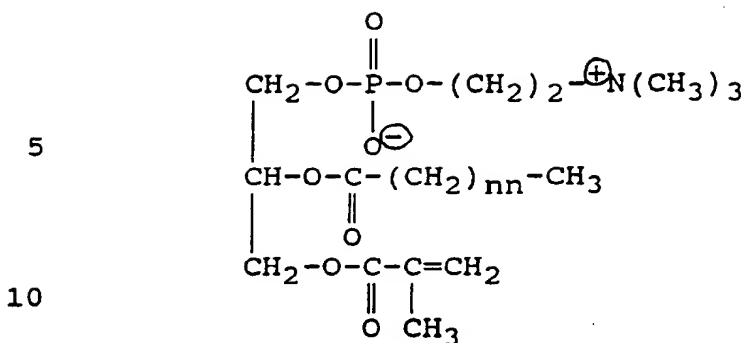


Compound C

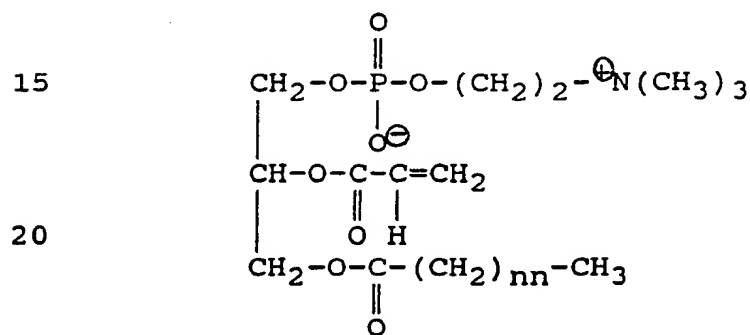


Compounds D

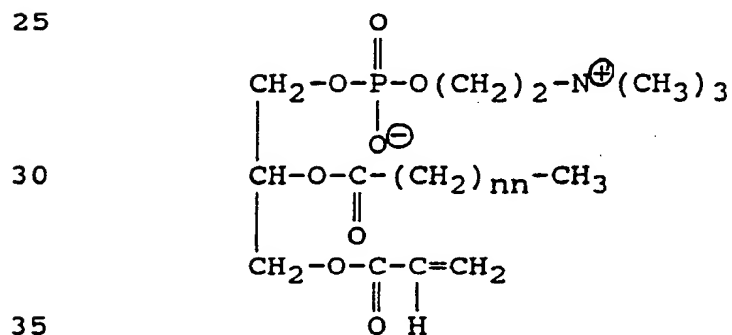
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Compounds E



Compounds F



Compounds G

Particular examples of preferred comonomers bearing a centre of permanent positive charge are

2(methacryloyloxy)ethyl-2'(trimethylammonium)ethyl

40 phosphate inner salt [Compound C above] and 1[4(4'-vinylbenzyloxy)butane]-2''(trimethylammonium)ethyl

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phosphate inner salt [a compound of formula (III)].

Comonomers bearing a centre of permanent positive charge, such as those of formulae (II) and (III), and comonomers of formula (V) may be prepared by conventional techniques using known reactions, for example using a suitable substituted alkyl (alk)acrylate, glycerophosphoryl choline or suitable substituted styrene as starting material.

Examples of suitable substituted alkyl (alk)acrylates include dimethylaminoethyl(meth)acrylate and 2-hydroxyethyl(meth)acrylate.

Comonomers of formula (II) or (III) containing a group of formula (IVA), (IVB) or (IVC) and comonomers of formula (V) including a group of formula (VIA), (VIB), and (VIC) may be prepared as described in Reference Examples 1 to 4 or by analogous known methods.

Comonomers of formula (II) or (III) containing a group of formula (IVD) and comonomer of formula (V) including a group of formula (VID) may be prepared by selective acylation of glycerophosphorylcholine or analogues thereof at the primary hydroxyl group with an activated acid derivative such as an acid anhydride $O[C(O)B^1CH_3]_2$ or an acid halide CH_3B^1COHal where B^1 is as defined above and Hal is halogen, followed by acylation of the secondary hydroxyl group with an appropriate acylating agent, for example methacryloyl chloride. Purification, for example

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by column chromatography on a suitable support, may be performed after each acylation or after the second acylation only. Suitable activated acid derivatives include acid anhydrides, acid halides, reactive esters and
5 imidazolides. The acylations may be performed in a suitable anhydrous, aprotic solvent, for example N,N-dimethylformamide, optionally in the presence of a suitable non-nucleophilic base, for example triethylamine.

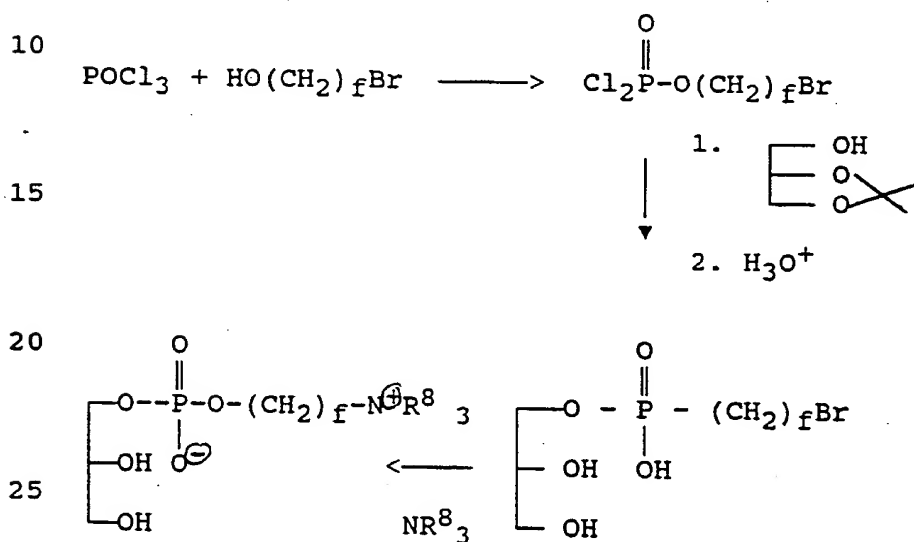
Alternatively, the primary alcohol group in
10 glycerophosphoryl choline or an analogue thereof may be blocked by reaction with a suitable protecting group reagent, for example t-butyldimethylsilyl chloride, under standard conditions and the secondary hydroxy group then treated with an acylating agent such as methacryloyl
15 chloride. The t-butyldimethylsilyl protecting group may be removed by treatment with a dilute organic or mineral acid, for example p-toluene sulphonic acid, hydrochloric acid or with tetra-butylammonium fluoride. The deblocked primary hydroxyl group may then be treated with an activated acid
20 derivative such as an acid anhydride $O[C(O)B^1CH_3]_2$ or acid halide CH_3B^1COHal where B^1 is as defined above, and Hal is halogen.

Analogues of glycerophosphorylcholine may be prepared by reaction of phosphorus oxychloride with a
25 bromoalcohol in an inert aprotic solvent, such as dichloromethane, to give a bromoalkylphosphorodichloridate.

- 20 -

The dichloro derivative thus produced may then be treated with 2,2-dimethyl 1,3-dioxolane-4-methanol in the presence of a base, for example triethylamine, followed by acid hydrolysis to give a bromoalkylphosphoroglycerol

5 derivative. This may then be treated with an amine NR^8_3 , where R^8 is as defined above, for example trimethylamine, to generate the glycerophosphorylcholine analogue. This preparation is depicted in the following scheme.



where R^8 and f are as defined in relation to groups of formula (IVD).

30 Comonomers of formula (II) or (III) containing a group of formula (IVE) and comomers of formula (V) containing a group of formula (VIE) may be prepared by the selective acylation of glycerophosphorylcholine or an analogue thereof at the primary hydroxyl group with for
35 example, methacryloyl chloride followed by reaction at the

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secondary hydroxyl group using an activated acid derivative, such as an acid halide $O[C(O)B^2CH_3]_2$ or an acid halide CH_3B^2COHal , where B^2 is as defined above and Hal is halogen. The intermediates and final products may
5 be purified, as necessary using column chromatography. Optionally, protecting group strategy, similar to that outlined above in relation to production of comonomers containing a group of formula (IVD), may be employed.

Comonomers of formula (II) or (III) containing a
10 group of formula (IVF) may be prepared in an analogous manner to comonomers containing groups of formula (IVD) or (IVE).

Crosslinking Comonomers

The copolymers of the invention also comprise
15 residues of difunctional and/or trifunctional comonomers. Such comonomers are capable of crosslinking the polymer during polymerisation. Conventional crosslinking agents may be used.

Examples of suitable crosslinking comonomers
20 include alkane diol or triol di- or tri(alk)acrylates, eg (meth)acrylates, preferably containing 1 to 8 carbon atoms in the diol or triol residue; alkylene di- or tri-(alk)acrylamides, e.g. (meth)acrylamides, preferably containing 1 to 6 carbon atoms in the alkylene group and
25 and di- or tri-vinyl compounds such as di- or tri-vinyl

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benzene compounds. Particular examples of crosslinking agents include ethyleneglycoldimethacrylate, tetraethyleneglycol dimethacrylate, trimethylolpropanetrimethacrylate and N,N-
5 methylenebisacrylamide.

Optionally the comonomer mixture used for polymerising the copolymer further comprises a gel swelling monomer such as an N-vinyl lactam, methacrylic acid or acrylic acid and where appropriate a bulking or solvating
10 agent such as a solvent, for example, an alcohol or water.

Polymers of the invention may be prepared by copolymerising monomers bearing a centre of permanent positive charge, diluent monomers and crosslinking monomers usually by bulk polymerisation in an appropriate mould.
15 Additionally a solvent or solvent mixture may be included to provide a suitable reaction medium for immiscible comonomers. Suitable solvents include water, halogenated organic solvents and non-halogenated organic solvents. Initiators and/or reagents to modify the bulk morphology of
20 the final polymer may also be included. Any conventional technique may be used for the polymerisation, typically thermal polymerisation or ultraviolet polymerisation.

The invention therefore further provides a method of preparing a crosslinked polymer which comprises
25 copolymerising a monomer composition, such as a monomer solution, comprising a diluent monomer or monomers, a

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comonomer or comonomers including within its structure a centre of permanent positive charge, and a monomer or monomers which will crosslink the resultant polymer.

Optionally, the monomer composition further comprises a solvent or solvent mixture and a polymerisation initiator or initiators.

The monomer composition which is subjected to polymerisation typically comprises at least 30%, preferably at least 60%, and up to 99.79% by weight of diluent monomer. It typically comprises at least 0.2% and up to 50% monomer or monomers which contain a centre of permanent positive charge and from 0.01% to 20% by weight of crosslinking monomer. Optionally up to 10% by weight of gel swelling monomer is included.

In one embodiment the monomer composition which is subjected to polymerisation typically comprises at least 70%, preferably at least 80% by weight of the diluent monomer. It further comprises at least 0.2% and up to 20% of monomer or monomers which bear a centre of permanent positive charge and, optionally, up to 10% by weight of gel-swelling monomer or monomers.

The monomer composition may comprise conventional further polymer ingredients such as cross-linking agents and polymerisation initiators. These further ingredients are in one embodiment used in a total amount from 0.1 to 5%, typically from 0.2 to 3% and preferably about 0.5% by

- 24 -

weight relative to the weight of the monomer composition prior to polymerisation.

Preferably the monomer composition comprises at least 0.01% and up to 10% of crosslinking monomer or
5 monomers.

Examples of suitable initiators include bis(4-tertiarybutylcyclohexyl)-peroxydicarbonate, benzoylperoxide, 2,2'-azo-bis(2-methylpropionitrile) [i.e. azo-bis-isobutyro nitrile], 1-benzyl-2-hydroxy-2-
10 dimethylethane-1-one and benzoin methylether. An initiator is generally used in a total amount from 0.1% to 5, typically from 0.2% to 3% and preferably about 0.5% by weight relative to the weight of the total monomer composition prior to polymerisation

15 Additionally the monomer composition may have added to it a solvent or solvent mixture. Examples of suitable solvents are ethanol, methanol and water. When present, solvent suitably comprises from 0.1 to 50 weight % of the total reaction mixture, preferably from 5 to 40 weight %.

20 The polymer is prepared by dissolving the monomer or monomers bearing the centre of positive charge in the diluent monomer or monomers or diluent monomer/solvent mixture together with the crosslinking monomer or monomers and if present the polymerisation initiator or initiators.
25 The solution thus formed is then purged with nitrogen, to remove any oxygen which may be present before the

- 25 -

polymerisation process is begun. Polymerisation is carried out in a sheet-forming mould, a contact lens precursor button (thick round disc) mould, a contact lens mould or to provide a cylindrical polymer rod. For example, when
5 carried out in a sheet-forming mould the monomer solution may be injected between two spaced plates and then polymerised in situ to generate a polymer sheet.

Generally the copolymers of the invention will be produced by copolymerisation in the absence water. This
10 produces a xerogel material which can be moulded into contact lenses directly or moulded to give contact lens buttons which can be lathe cut using methods known in the art to produce contact lenses. The xerogel material may be washed in water or in aqueous buffer to remove any excess
15 monomer and initiator. The xerogel material can be subsequently hydrated to produce hydrogel with an equilibrium water content of up to 90%, and preferably from 30 to 80%.

The polymers of the invention are both transparent
20 and water swellable and therefore suitable for use as contact lens materials. In particular, the polymer may be suitable for use in contact lenses which are for example soft or gas permeable contact lenses.

The invention further provides contact lenses made
25 from polymers of the invention as hereinbefore defined.

The invention may be further illustrated by the

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following examples.

Example 1

Formation of 2(methacryloyloxyethyl)-

2'(trimethylammonium)ethyl phosphate inner salt -co- 2-

5 hydroxyethylmethacrylate -co- ethyleneglycoldimethacrylate
buttons

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl
phosphate inner salt (compound C) (4.86g) was dissolved in
2-hydroxyethylmethacrylate (14.8g), together with
10 ethyleneglycoldimethacrylate (0.25g) and bis(4-
tertiarybutylcyclohexyl)-peroxydicarbonate (0.048g). This
solution was de-gassed with nitrogen gas and then pipetted
into an open stainless steel contact lens button mould.
The mould was placed in an oven in a nitrogen atmosphere at
15 50°C for 1 1/4 hours. After this time the mould was
removed. The buttons were pushed out of the mould and the
reaction completed by heating at 70°C in a vacuum oven for
24 hours. The buttons were optically clear and could be
machined to make contact lenses.

20

Example 2

Formation of 2(methacryloyloxyethyl)-2'(trimethyl-

ammonium)ethyl phosphate inner salt -co- 2-

hydroxyethylmethacrylate -co- ethyleneglycoldimethacrylate

25 buttons by photopolymerisation

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl

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phosphate inner salt (compound C) 5.00g was dissolved in 2-hydroxyethylmethacrylate (14.2g) together with ethyleneglycoldimethacrylate (0.2g), 1-benzyl-2-hydroxy-2-dimethylethane-1-one (0.2g) and bis(4-
5 tertiarybutylcyclohexyl)-peroxydicarbonate (0.02g). The solution was de-gassed with N₂ and then pipetted into an open stainless steel contact lens button mould. The monomer solutions were irradiated with a 100 w/inch medium pressure, mercury vapour lamp for 2 minutes. The reaction
10 was completed thermally at 70°C in a vacuum oven for 24 hours. The resulting buttons were machined to make contact lenses.

Example 3

15 Formation of 2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt -co- methylmethacrylate -co- ethyleneglycoldimethacrylate buttons

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (5.76g) was dissolved in ethanol
20 (6.5ml) and methylmethacrylate (7.5g). Ethyleneglycoldimethacrylate (0.21g), 1-benzyl-2-hydroxy-2-dimethylethane-1-one (0.2g) and bis(4-tertiarybutylcyclohexyl)-peroxydicarbonate (0.01g) were added to the solution and dissolved. The resulting solution
25 was degassed with the gas and poured into an open stainless steel contact lens button mould. The solutions were then

- 28 -

irradiated by a 100 W/inch medium pressure mercury vapour lamp for 2 minutes. The reaction was completed thermally at 70°C in a vacuum oven for 24 hours. The ethanol was removed from these buttons by heating at 80°C for 48 hours in a vacuum oven. The resulting buttons were machined to make contact lenses.

Example 4

Formation of 2(methacryloyloxyethyl)-

2'(trimethylammonium)ethyl phosphate inner salt -co-

10 methylmethacrylate -co- ethyleneglycodimethylacrylate rod

A xerogel rod (1cm diameter x 10cm) was produced as follows:-

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (compound C) (5.77g) was mixed with ethanol (6.5g), methylmethacrylate (7.4g), ethyleneglycoldimethacrylate (0.2g) and bis(4-tertiarybutylcyclohexyl)-peroxydicarbonate (0.03g). The mixture was added to a polypropylene tube (1cm diameter x 10cm) which was sealed at one end. N₂ gas was bubbled through the solution and then a cap placed over the end of the tube. The tube was then placed in an oven at 50°C for 1.5 hours. After this time the gelled rod of polymer was removed from the tube.

The reaction was completed at 70°C for 24 hours.

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After this time the rod was cut into 1cm cylinders. These cylinders were heated in a vacuum oven at 80°C for 48 hours in order to removed the ethanol. The resulting buttons were machined into lenses.

5

Example 5

Formation of 2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt -co- 2-hydroxyethylmethacrylate -co- ethyleneglycoldimethacrylate membrane

10 2(methacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt (compound C) (3.60g) was dissolved in 2-hydroxyethylmethacrylate (6.27g) together with ethyleneglycoldimethacrylate (0.12g) as a crosslinking agent and azobisisobutyronitrile (0.2g) as a polymerisation
15 initiator. The resultant monomer solution was then deoxygenated by bubbling nitrogen through for 5 minutes.

The monomer solution thus prepared was injected into a mould formed by two glass sheets covered by spray mounted polyethyleneterephthalate sheet and separated using
20 a polytetrafluoroethylene spacer. Polymerisation was carried out in situ by heating the mould to 80°C for 2 hours.

The polymer sheet thus formed was removed from the mould and swollen with water or a borate buttered saline
25 solution at pH 7.1 to form a hydrogel sheet. The starting formulation is suitable for the mould polymerisation of

- 30 -

soft contact lenses.

Example 6

Formation of 2(methacryloyloxyethyl)-2'(trimethyl
ammonium)ethyl phosphate inner salt-co-2-hydroxy ethyl-
5 methacrylate-co-methylmethacrylate-co-ethyleneglycol-
dimethacrylate membrane

The method of Example 5 was repeated just using
2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl
phosphate inner salt (compound C) (3.79g), in 2-
10 hydroxyethyl-methacrylate (8.39g) together with
methylmethacrylate (5.04g), ethyleneglycoldimethacrylate
(0.254g) as crosslinking agent and azobisisobutyronitrile
(0.15g) as a polymerisation initiator.

The resultant hydrogel sheet is similar to that
15 obtained in Example 5. The starting formulation is
suitable for the mould polymerisation of soft contact
lenses.

Example 7

Formation of 2-(trimethylammonium)ethyl methacrylate
20 trifluoromethane sulphate -co- 2-hydroxyethylmethacrylate
-co- methylene bis-acrylamide polymer sheet

2-(trimethylammonium)ethyl methacrylate trifluoro-
methanesulphonate, compound A, (0.25 g) was dissolved in

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hydroxyethyl methacrylate (5 g) together with methylene bis-acrylamide (25 mg) as cross-linking agent and benzoyl peroxide (25 mg) as polymerisation initiator. The resulting monomer solution was then deoxygenated by
5 bubbling nitrogen through for 5 minutes.

The monomer solution thus prepared was injected into a mould formed by two silylated glass plates separated by a teflon spacer. Polymerisation was carried out in situ by heating the mould to 70°C and maintaining it at that
10 temperature for 2 hours.

The polymer sheet formed was removed from the mould and swollen with water or a saline solution to form a hydrogel sheet, which is a material suitable for forming into soft contact lenses.

15 Example 8: Preparation of further copolymers

The method of Example 6 was repeated using, respectively, each of compounds B and C and compound types D to G prepared as described in the Reference Examples in place of compound A. The hydrogel sheet formed in each
20 case was suitable for forming into soft contact lenses.

Mechanical testing of copolymers

The copolymer sheets and lenses produced may be swelled in appropriate aqueous solutions and then dehydrated by heating. The water content may be determined
25 by weight.

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Tear strength measurement may be performed by Instron analysis using appropriate ASTM procedures. Oxygen permeability may be determined with appropriate electrodes in accordance with appropriate ASTM standards. The absorption of tear proteins by the copolymers may be measured by standard spectrophotometric techniques.

Example 9Lathe cutting to produce contact lenses

Buttons (as prepared in Example 1) were mounted using a low melting point wax and cut with a lathe speed of 2800 rpm to produce contact lenses. Cutting times were 1-2 seconds for 0.01 mm thickness reduction from the edge to the centre. Nitrogen may be used to cool the diamond button interface. The contact lenses produced were cleaned with petroleum ether (60-80) and polished with an oil based polish (SP2).

Example 10Protein adsorption and equilibrium water content study

Two hydrogel membranes of comparable water content were prepared: membrane A (comparative) comprised of methacrylic acid (16.5 mole%), 2-hydroxyethylmethacrylate, (83.3 mole%) and ethyleneglycol dimethacrylate (0.2 mole %); membrane B according to the invention comprised of 2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (40% mole), methylmethacrylate (59

- 33 -

mole%) and ethylene glycol dimethacrylate (1%). Both membranes were cut into 0.9mm discs and soaked in a buffered protein solution for 24 hours at 35°C. Control lenses were soaked in buffer solution for the same length
5 of time. The buffer solution was the same as that of the buffered protein solution except that the bovine albumin and chicken lysozyme were not added.

The composition of the buffered protein solution was as follows:

10	Sodium Chloride	0.85%
	Boric Acid	0.46%
	Sodium Borate (10 H ₂ O)	0.04%
	Bovine Albumin	0.39%
	Chicken Egg Lysozyme	0.12%
15	Water	98.4%

The conditions chosen mimic the ocular environment and are equivalent to those experienced by a contact lens during 7 days wear. The equilibrium water content was measured thermogravimetrically and the dry weights of the
20 membranes compared after soaking in the buffer solution and the buffered protein solution.

The equilibrium water content data and changes in dry weight equivalent to the adsorption of protein from the solution are shown below:

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	<u>Membrane</u>	<u>Equilibrium Water</u>	<u>Increase in Dry</u>
		<u>Content %</u>	<u>Weight (g. Protein/g</u> <u>Polymer</u>
5	A at 35°C	79.4 ± 0.6	-
	A at 35°C in protein solution	75.9 ± 0.9	0.13 ± 0.04
10	B At 35°C	70.5 ± 0.4	-
15	B At 35°C in protein solution	71.1 ± 0.5	0.01 ± 0.05

The membrane containing 2(methacryloyloxy-ethyl)-2'(trimethylammonium) ethyl phosphate inner salt was found to absorb significantly less protein than a membrane material of comparable water content. The equilibrium water content also remained unchanged.

Reference Example 1:

Synthesis of 2(trimethylammonium)ethylmethacrylate

trifluoromethanesulphonate (Compound A)

25 2(Dimethylamino)ethylmethacrylate was vacuum distilled and then dissolved in 0.1M dichloromethane. Methyltrifluoromethyl sulphonate (one molar equivalent) was added slowly to the resulting solution, the temperature of the solution being maintained throughout at 40°C or less.

30 The product precipitated out slowly and was recovered by

- 35 -

filtration and washed in cold dichloromethane. The synthesis is depicted in Reaction Scheme B.

Reference Example 2:

Synthesis of dimethyl(2-methacryloxyethyl)-(1(2-

5 sulphopropyl)) ammonium betaine inner salt (Compound B)

2(Dimethylamino)ethylmethacrylate was vacuum distilled and then dissolved in 0.1M dichloromethane. To this solution was added an equimolar amount of propane sultone. The betaine slowly precipitated out of solution
10 and was recovered by filtration and washed with cold dichloromethane. The reaction is shown in Reaction Scheme B.

Reference Example 3

Preparation of 2(methacryloyloxyethyl)-2'(trimethylammonium

15 ethyl phosphate inner salt (Compound C)

The preparation is illustrated by the reaction scheme C which follows.

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a) 2-Chloro-1,3-dioxaphospholane (1)

In a flask fitted with a pressure equalising dropping funnel, reflux condenser (fitted with a CaCl_2 guard tube) and magnetic stirrer, was placed a solution of phosphorus trichloride (220ml; 346.3g; 2.52mol) in dichloromethane (500ml). Ethylene glycol (139ml; 154.7g, 2.49mol) was then added dropwise via the dropping funnel at such a rate that the evolution of HCl did not become too excessive. On the addition of the ethylene glycol, the condenser was arranged for distillation, and the dichloromethane removed at atmospheric pressure. When the distillate temperature reached 60°C the flask was arranged for vacuum distillation using a water pump, Distillation then gave 2-chloro-1,3-dioxaphospholane (158ml; 224.5g; 71.3%) as a colourless mobile liquid (which fumes in moist air) b.pt. 36-40°C/21mm Hg. [cf 45.5-47°C/20mm Hg, Lucas et al, J. Am. Chem. Soc., 72, 5491, (1950)].

IR (cm^{-1} , thin film) 2980, 2905, 1470, 1210, 1005, 930, 813, 770.

b) 2-Chloro-2-oxo-1,3,2-dioxaphospholane (2)

In a flask fitted with a magnetic stirrer, reflux condenser (fitted with a CaCl_2 guard tube) and sintered glass gas inlet tube, was placed a solution of 2-chloro-1,3,2-dioxaphospholane (100.8g; 0.797mol) in dry benzene (200ml). The solution was stirred and a steady stream of oxygen was bubbled through the solution. The reaction was

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mildly exothermic, and temperature control was achieved by allowing the solvent to reflux. The oxygen was passed through the reaction mixture for 6 hours. The solvent was removed by rotary evaporation, and the colourless mobile
5 residue distilled to give 2-chloro-2-oxo-1,3,2-dioxaphospholane (2) (87.41g; 77%) as a colourless mobile liquid -b.pt 95-97°C/0.2mbar [c.f. 102.5-105°C/1mbar (Edmundson, Chem. Ind. (London)), 1828 (1962); 79°C/0.4mbar (Umeda et al., Makromol. Chem. Rapid Commun., 3, 457,
10 (1982)].
IR(cm^{-1} , thin film) 2990, 2910, 1475, 1370, 1310, 1220, 1030, 930, 865, 830.

c) 2(2-Oxo-1,3,2-dioxaphospholan-2-yloxy)ethyl methacrylate
(3)

15 In a flask fitted with a magnetic stirrer, low temperature thermometer, and a pressure equalising funnel fitted with a silica gel guard tube, was placed a solution of 2-hydroxyethylmethacrylate (20.00g, 0.154mol) and triethylamine (15.60g; 0.154mol) in dry diethyl ether
20 (300ml). The solution was stirred and cooled to between -20°C and -30°C. A solution of freshly distilled 2-chloro-2-oxo-1,3,2-dioxaphospholane(2) (21.9g; 0.154 mol) in dry diethyl ether (20ml) was then added dropwise over 30 minutes, the temperature being held at -20°C during the
25 addition. Stirring was continued at this temperature for a

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further 1 hour and then for a further hour as the reaction mixture was allowed to warm to room temperature. The precipitated triethylamine hydrochloride was removed by filtration, and was washed well with dry ether. The ether was removed from the combined filtrate and washings by rotary evaporation. The cloudy oil residue was then shaken for 5 minutes with dry diethyl ether (50ml) to precipitate a further crop of triethylamine hydrochloride, which was again removed by filtration. Removal of the ether on the rotary evaporator gave (3) (34.18g; 94.3%) as a colourless viscous oil.

IR (cm^{-1} , thin film) 1720, 1640, 1450, 1360, 1310, 1290, 1170, 1030, 930, 850.

NMR (CDCl_3 ; 60MHz, δ ppm) 1.95 (s, 3H), 4.25-4.70 (m, 8H), 5.70 (m, 1H), 6.25 (m, 1H).

Rf (SiO_2 , eluting with 10% MeOH:90% CH_2Cl_2 -0.9; spot visualised with molybdenum blue spray reagent (eg Sigma), and with iodine vapour).

d) 2(Methyacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt (4).

The phospholane (3) (67.20g; 0.285 mol) was dissolved in 100 ml of dry acetonitrile, and placed in a heavy walled tissue culture bottle. The phospholane solution was then treated with a solution of anhydrous trimethylamine (25.74g; 0.436 mol) in dry acetonitrile

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(100ml). The vessel was then sealed, and placed in a water bath held at 50°C for 30 hours. The vessel was opened, and the solution brought to the boil. The solution was filtered whilst hot, and then set aside for

5 crystallisation.

The product was collected by filtration, and most of the solvent removed by suction. The wet product was then washed thoroughly with anhydrous ether, then dried in vacuo, to give (4) as a white amorphous, hygroscopic solid
10 (51.16g; 61%). Evaporation of the mother liquor gave a very viscous oil (20.00g; 23%), from which further product (4) crystallised on standing at -20°C TLC (silica gel plates, eluting with MeOH/CH₂Cl₂ (1:1 v/v)) showed one spot R_f 0.1, which was revealed with Dragendorffs reagent, Molybdenum
15 blue spray reagent, and iodine vapour.

IR(cm⁻¹ 1720, 1640, 1320, 1300, 1230, 1170, 970, 750.

NMR (D₂O; 60MHz; δ ppm) 2.0 (s, 3H), 3.27 (s, 9H) 3.60-4.50 (m, 8H), 5.80, (m, 1H) and 6.25 (m, 1H).

CHN Found: C 42.98%, H 7.88%, N 4.42%, P 10.51%.

20 CHN Theory: C 44.75%, H 7.46%, N 4.75%, P 10.51%.

(d1) 2-(Methacryloyloxyethyl)-2'-(trimethylammonium)ethyl phosphate inner salt [Alternative Preparation]

Into a glass pressure bottle (300cm³), were placed 2-(2-oxo-1,3,2-dioxaphospholan-2-yloxy)ethyl methacrylate
25 (10.0 g, 42 mmol) prepared in step (c) and dry acetonitrile

- 40 -

(60cm³). The pressure bottle was cooled in cold water and then trimethylamine (2.5 g, 42 mmol) was rapidly added to the cold solution. The pressure bottle was closed and then shaken in a thermostat maintained at 55°C for 2 hours. It was then allowed to come to room temperature and to stand overnight, and was shaken again at 55°C for 13 hours. After the reaction it was cooled down in water to 10°C. It was rapidly filtered with filter paper. The filtrate was evaporated under reduced pressure with a stream of nitrogen for 2 hours to afford the product (12.3 g, 98%) as a colourless viscous liquid which crystallised on standing in a freezer. The product could be purified by preparative liquid chromatography.

Reference Example 4:

15 1-alkanoyl-2-methacroyl phosphatidyl choline and
1-metharyloyl-2-alkanoyl phosphatidyl choline
(Compound types D and E)

Glycerophosphorylcholine (0.01 mole), obtained by base hydrolysis of natural phosphatidylcholine, may be stirred with alkynoic acid anhydride (0.01 mole) and dimethylamino pyridine (0.01 mole) in dimethylsulphoxide (150 cm³).

At the conclusion of this reaction further dimethylamino pyridine (1 mole) together with methacrylic acid anhydride (1 mole) may be added. The resulting

25

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mixture may be stirred for 24 hours. The phosphatidylcholine formed may be purified by column chromatography on silica using a gradient elution procedure with chloroform: methanol: water.

- 5 The synthesis is depicted in reaction scheme D in which $R = CH_3$.

Reference Example 5:

- Synthesis of 1-alkanoyl-2-acroyl phosphatidylcholine and 1-acroyl-2-alkanoyl phosphatidylcholine (Compounds type F
10 and G)

The procedure of Reference Example 4 may be repeated, but with acrylic acid anhydride (1 mole) being used in place of methacrylic acid anhydride. The synthesis is depicted in Reaction Scheme D in which $R = H$.

- 15 Reference Example 6

Preparation of 1[4(4'-vinylbenzyloxy)butane]-2"-
(trimethylammonium)ethyl phosphate inner salt.

The synthesis is depicted in Reaction Scheme E.

4-Hydroxy-1(4'-vinylbenzyloxy)butane (5)

- 20 1,4-Butanediol (50.00g) was dissolved in dry toluene (60ml), para-choloromethylstyrene (15.62g; 0.1mol) was then added with stirring. A catalytic quantity of 18-crown-6 (0.3g) was then added. The flask was stoppered, stirred at room temperature for 18 hours and for a further

- 42 -

4 hours at 45-60°. The resulting solution was then poured in to water (500ml) and extracted with dichloromethane (3x75ml). The combined extracts were dried (MgSO₄) and evaporated (20°/21mm) to give a yellow oil, which was
5 distilled to give a yellow oil (14.33g; 69.6%).b.pt. 152-157°/1mbar.

NMR (60MHz: CDCl₃) 1.55 (m, 4H); 3.50 (m, 5H, 1H exch); 4.45, (s, 2H) 5.50 (dd, 2H), 6.75 (dd, 1H), 7.40 (m, 4H). IR (thin film), 3402, 2938, 2888, 1631, 1602, 1582, 1511,
10 1480, 1445, 1382, 1320, 1116, 1063, 920, 907, 827, 801, 716 and 667 cm⁻¹.

4(2-Oxo-1,3,2-dioxaphospholane-2-yloxy)-1(4'-vinylbenzyloxy)butane (6)

4-Hydroxy-1(4'-vinylbenzyloxy)butane (5) (10.03g; 48.69
15 mmol) and dried triethylamine (4.92g, 48.69 mmol) were dissolved in dry diethyl ether (150ml) and the resulting solution placed in a rigorously dried flask. The solution was cooled to -30° and 2-chloro-2-oxo-1,3,2-dioxaphospholane (6.94g; 48.69 mmol) added dropwise over 30
20 minutes, the temperature being held at -30°. The reaction mixture was then stirred for a further 2 hours, during which time the temperature was allowed to rise to 10°. The mixture was filtered and the precipitate washed with dry ether. The filtrate was evaporated (20° / 21mm) to give a
25 cloudy oil. The residue was shaken with 50ml of dry ether and refiltered. Evaporation of the filtrate gave the

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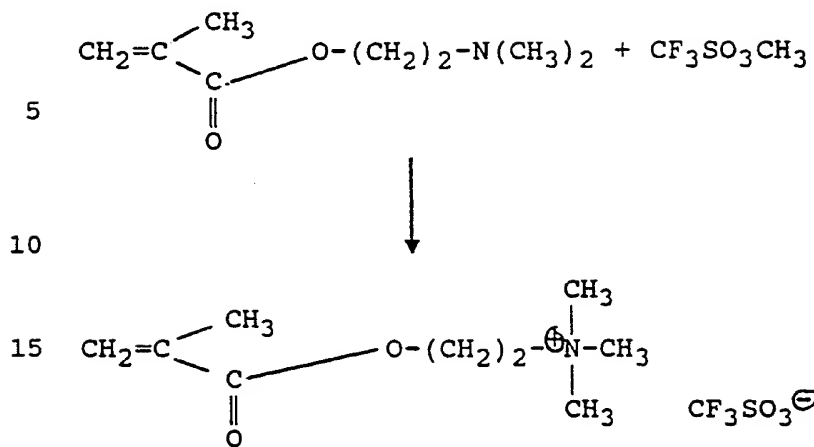
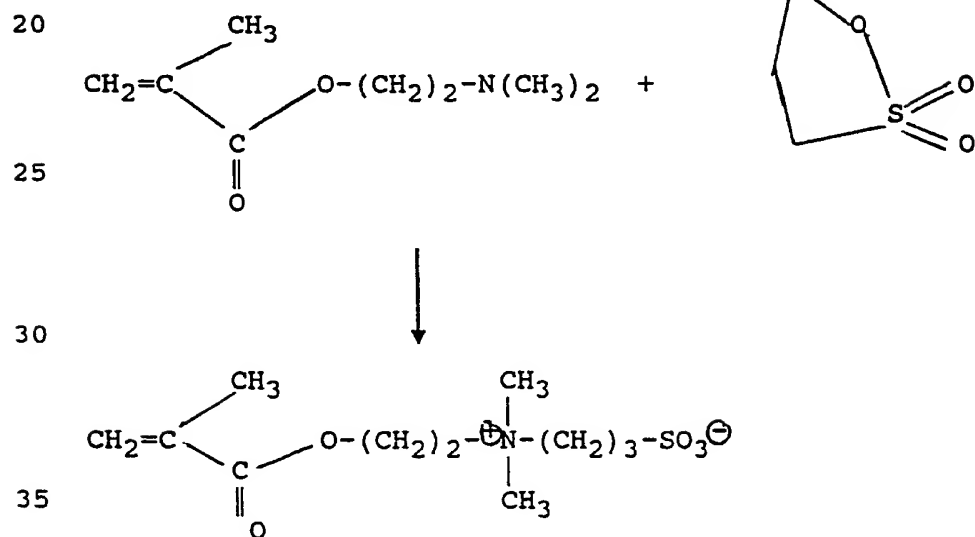
product as a viscous yellow oil (13.73 g; 90.4%).

TLC (eluting with 10% MeOH/ 90% dichloromethane) showed one major spot, which stained with acid molybdate reagent (R_f 0.61), IR (thin film) 3458, 2945, 2917, 2860, 5 1630, 1602, 1581, 1475, 1419, 1363, 1283, 1103, 1032, 820, 842, 807, 800, 715, 610 and 421 cm^{-1} .

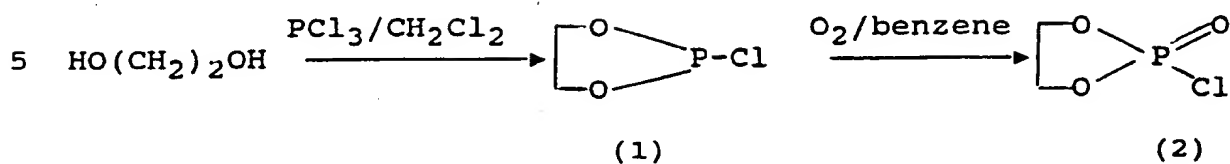
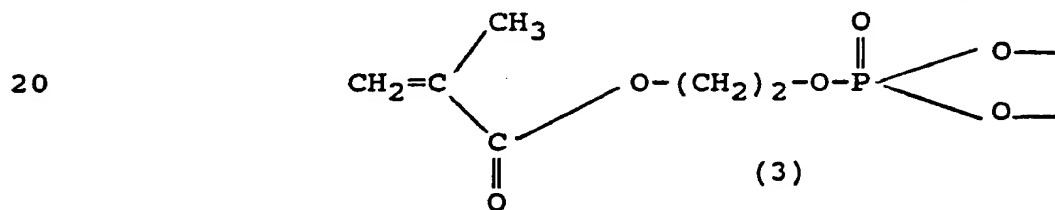
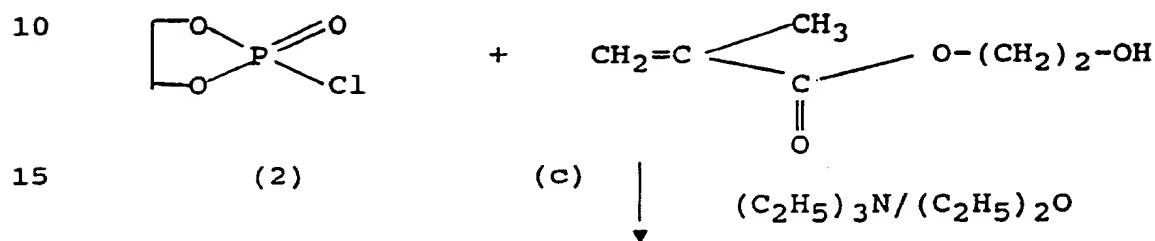
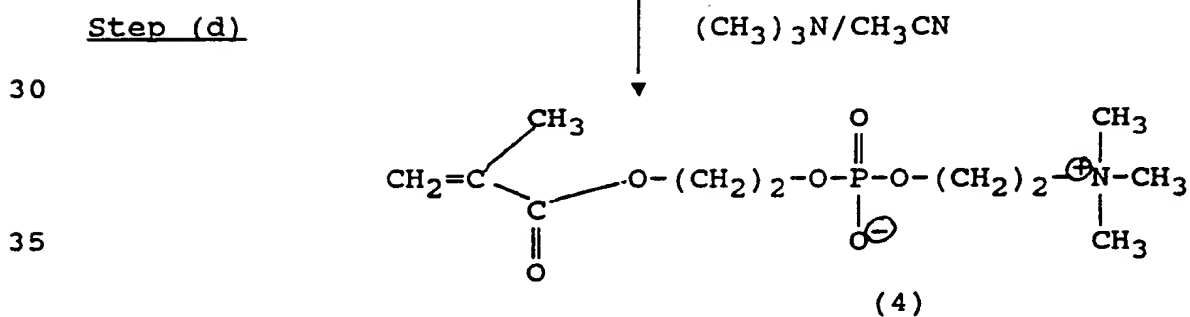
1[4(4'-Vinylbenzyloxy)butane]-2"(trimethylammonium)ethyl phosphate inner salt (7)

Trimethylamine (2.00g, 33.9 mmol) was distilled 10 into a reaction vessel, and frozen with liquid nitrogen. A solution of the 4(2-oxo-1,3,2-dioxaphospholane-2-yloxy)-1-(4'-vinylbenzyloxy)butane (6) (10.00g, 32.1 mmol) in anhydrous acetonitrile (40ml) was then added to the reaction vessel, which was then sealed and placed in a 15 thermostatted water bath (50° for 50 hours). The reaction vessel was then cooled to room temperature, opened, and the reaction mixture evaporated to about half its original volume (21 mm pressure). The concentrated solution was then stirred at room temperature, whilst anhydrous ether 20 (200ml) was added dropwise to precipitate the product as a viscous oil. The mixture was then left for several hours at -10° . The product was collected by decanting off the supernatant solid. TLC (eluting with methanol/dichloromethane 1:1) showed one major spot at R_f 25 0.0-0.1 which stained with both Dragendorffs reagent and acid molybdate.

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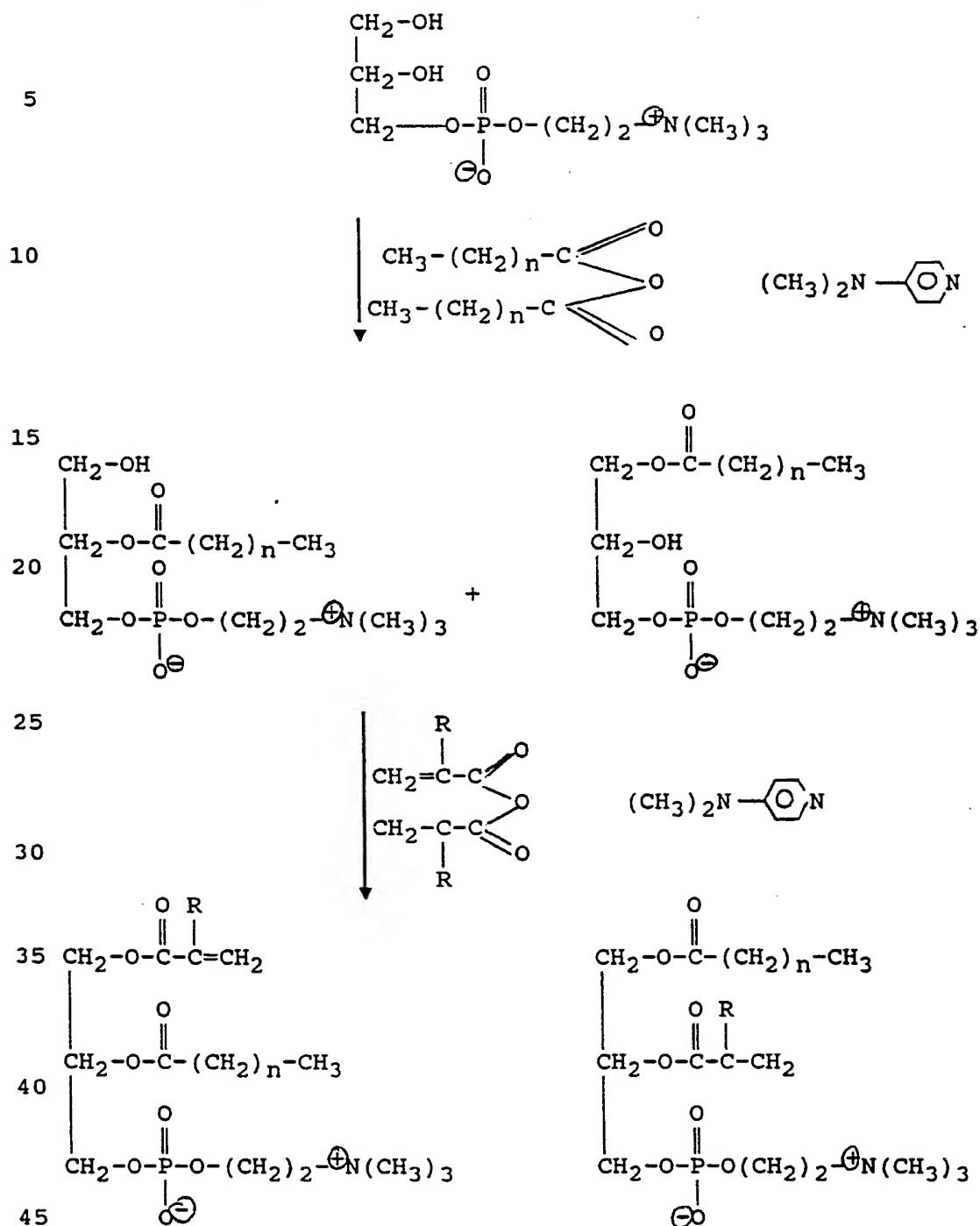
Reaction Scheme AReaction Scheme B

- 45 -

Reaction Scheme CStep (a)Step (b)Step (c)Step (d)

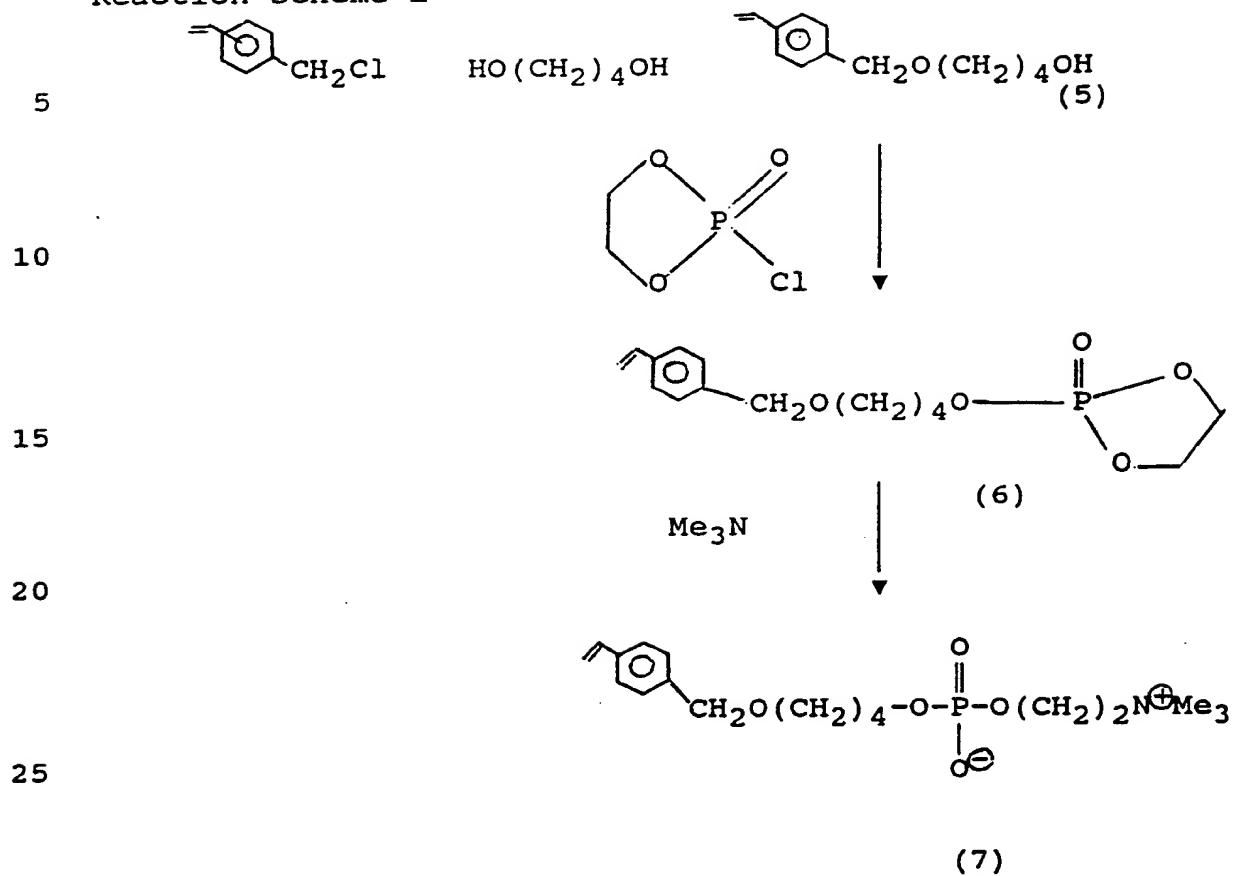
Steps (a) to (d) correspond with the steps in Reference Example 4

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Reaction Scheme D

- 47 -

Reaction Scheme E



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CLAIMS

1. A crosslinked copolymer which is obtainable by polymerising a neutral diluent monomer or monomers, a monomer or monomers bearing a centre of permanent positive charge, and a bifunctional or trifunctional crosslinking agent.

2. A copolymer according to claim 1 in which the diluent monomer is selected from alkyl (alk)acrylates, dialkylamino alkyl (alk)acrylates, alkyl (alk)acrylamides hydroxyalkyl (alk)acrylates, N-vinyl lactams, styrene, substituted styrene derivatives; and mixtures thereof.

3. A copolymer according to claim 2 in which the diluent monomer is selected from vinylpyrrolidone, 2-hydroxyethylmethacrylate, methylmethacrylate and mixtures thereof.

4. A copolymer according to any one of the preceding claims in which the permanent positive charge in the comonomer or comonomers bearing a centre of positive charge is provided by a quaternary nitrogen atom.

5. A copolymer according to any one of the preceding claims which is obtainable by copolymerising a monomer bearing a centre of permanent positive charge of formula (I)



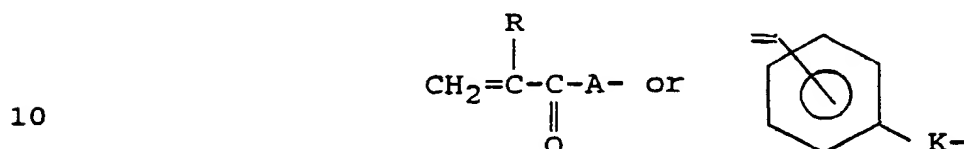
wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain or if X contains a carbon-carbon chain between B and the centre of

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permanent positive charge or if Y contains a terminal carbon atom, a valence bond,

X is a group bearing a centre of permanent positive charge and

5 Y is an ethylenically unsaturated polymerisable group selected from



wherein:

R is hydrogen or a C₁-C₄ alkyl group;

A is -O- or -NR¹- where R¹ is hydrogen or a C₁-C₄ alkyl group or R¹ is -B-X where B and X are as defined above; and

K is a group -(CH₂)_pOC(O)-, -(CH₂)_pC(O)O-, -(CH₂)_pOC(O)O-, -(CH₂)_pNR²-, -(CH₂)_pNR²C(O)-, -(CH₂)_pC(O)NR²-, (CH₂)_pNR²C(O)O-, -(CH₂)_pOC(O)NR²-, 20 -(CH₂)_pNR²C(O)NR²- (in which the groups R² are the same or different), -(CH₂)_pO-, -(CH₂)_pSO₃-, or, optionally in a combination with B, a valence bond, and p is from 1 to 12 and R² is hydrogen or a C₁-C₄ alkyl group.

6. A copolymer according to claim 5 in which B is 25 an alkylene group of formula -(CR³₂)_a-, wherein the groups -(CR³₂)- are the same or different, and in each group -(CR³₂)- the groups R³ are the same or different and each group R³ is hydrogen or C₁-C₄ alkyl, and a is from 1 to 12;

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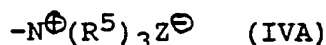
an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety,

an oligo-oxaalkylene group of formula

$-[(\text{CR}^4_2)_b\text{O}]_c(\text{CR}^4_2)_b-$ where the groups $-(\text{CR}^4_2)-$ are the same or different and in each group $-(\text{CR}^4_2)-$ the groups R^4 are the same or different and each group R^4 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl, and b is 2 or 3 and c is from 2 to 11,

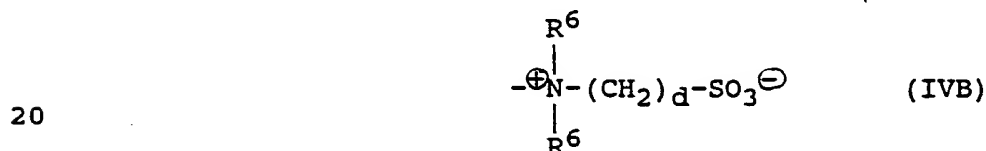
or if X contains a carbon-carbon chain between B and the centre of positive charge, or if Y contains a terminal carbon atom, a valence bond.

7. A copolymer according to claim 5 or 6 in which X is a group of formula (IVA)



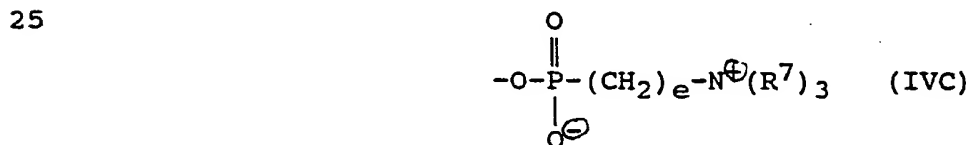
where the groups R^5 are the same or different and each is hydrogen or $\text{C}_1\text{-C}_4$ alkyl and Z^{\ominus} is a counter ion;

a group of formula (IVB):



where the groups R^6 are the same or different and each is hydrogen or $\text{C}_1\text{-C}_4$ alkyl and d is from 2 to 4;

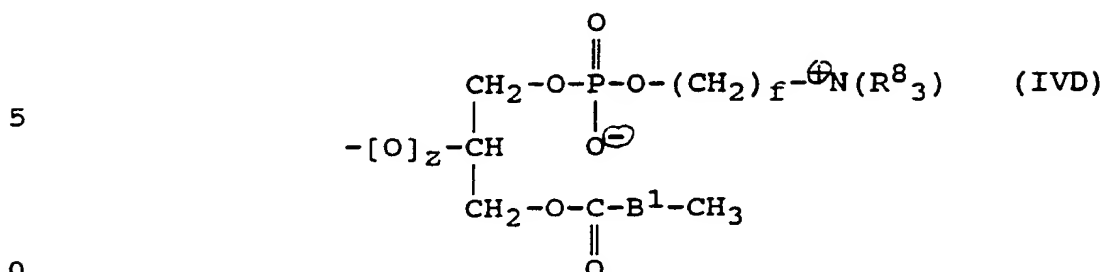
a group of formula (IVC):



where the groups R^7 are the same or different and each is hydrogen or $\text{C}_1\text{-C}_4$ alkyl, and e is from 1 to 4;

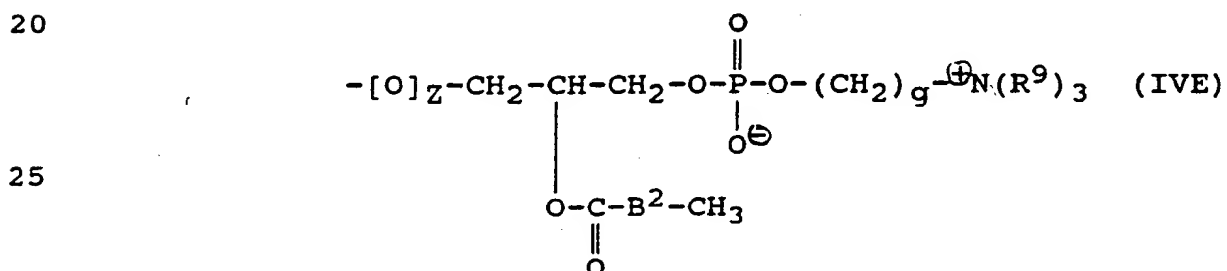
- 51 -

a group of formula (IVD):



wherein the groups R^8 are the same or different and each is hydrogen or C_{1-4} alkyl, B^1 is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, f is from 1 to 4 and if B is other than a valence bond, Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1;

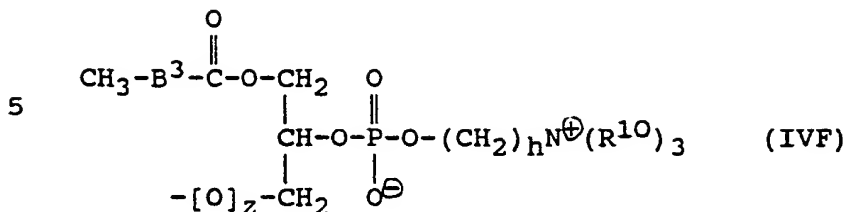
a group of formula (IVE):



wherein the groups R^9 are the same or different and each is hydrogen or C_{1-4} alkyl, B^2 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, g is from 1 to 4 and if B is other than a valence bond, Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1; or

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a group of formula (IVF):



wherein the groups R^{10} are the same or different and each
 10 is hydrogen or C_{1-4} alkyl, B^3 is a valence bond or a
 straight or branched alkylene, oxaalkylene or oligo-
 oxaalkylene group, h is from 1 to 4 if B is other than a
 valence bond, Z is 1 and if B is a valence bond Z is 0 if X
 is directly bonded to an oxygen or nitrogen atom and
 15 otherwise Z is 1.

8. A copolymer according to claim 7 in which X is
 a group of formula (IVD), (IVE) or (IVF) and B^1 , B^2 or B^3
 respectively contains up to 24 carbon atoms.

9. A copolymer according to claim 7 in which X is
 20 a group of formula (IVA), (IVB) or (IVC).

10. A copolymer according to claim 9, 8 in which
 the group X is a group of formula (IVC).

11. A copolymer according to claim 10 wherein the
 groups R^7 are all methyl.

25 12. A copolymer according to claim 11 which
 comprises residues of 2(methacryloyloxy)ethyl-2'-
 (trimethylammonium)ethyl phosphate inner salt.

13. A contact lens material comprising a copolymer
 according to any one of claims 1 to 12.

30 ~~14. A contact lens comprising a copolymer~~

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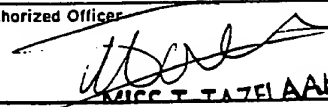
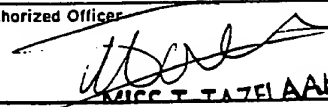
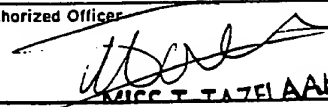
14. A contact lens comprising a copolymer according to any one of claims 1 to 12 or a contact lens material according to claim 13.

15. A process for producing a copolymer claimed in
5 any one of claims 1 to 12 which comprises copolymerising a monomer composition comprising a diluent monomer or monomers, a comonomer or comonomers bearing a centre of permanent positive charge, and a monomer or monomers which will crosslink the resultant polymers.

10 16. Use of a copolymer according to any one of claims 1 to 12 or a contact lens material according to claim 13 in the production of a contact lens.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01887

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 08 F 212/14, 220/34, G 02 B 1/04														
II. FIELDS SEARCHED <div style="text-align: center;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: none; vertical-align: bottom;">C 08 F; G 02 B</td> </tr> </table> <div style="text-align: center; font-size: small;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div>			Classification System	Classification Symbols	IPC5	C 08 F; G 02 B								
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IPC5	C 08 F; G 02 B													
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category *</th> <th style="width: 60%;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4038264 (ROSTOKER ET AL) 26 July 1977, see column 9, line 3 - column 10, line 60; abstract <div style="text-align: center;">--</div></td> <td style="vertical-align: top;">1-7, 9, 13-16</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">US, A, 4152508 (ELLIS ET AL) 1 May 1979, see column 4, line 24 - line 64; abstract <div style="text-align: center;">--</div></td> <td style="vertical-align: top;">1-7, 9, 13-16</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="vertical-align: top;">EP, A2, 0032443 (COOPERVISION U.K. LIMITED) 22 July 1981, see the whole document <div style="text-align: center;">--</div></td> <td style="vertical-align: top;">1-16</td> </tr> </tbody> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4038264 (ROSTOKER ET AL) 26 July 1977, see column 9, line 3 - column 10, line 60; abstract <div style="text-align: center;">--</div>	1-7, 9, 13-16	X	US, A, 4152508 (ELLIS ET AL) 1 May 1979, see column 4, line 24 - line 64; abstract <div style="text-align: center;">--</div>	1-7, 9, 13-16	A	EP, A2, 0032443 (COOPERVISION U.K. LIMITED) 22 July 1981, see the whole document <div style="text-align: center;">--</div>	1-16
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> Date of the Actual Completion of the International Search 28th January 1992 </td> <td style="width: 50%; border: none; vertical-align: top;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: large;">12 FEB 1992</div> </td> </tr> <tr> <td style="width: 50%; border: none; vertical-align: top;"> International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div> </td> <td style="width: 50%; border: none; vertical-align: top;"> Signature of Authorized Officer <div style="text-align: center;">  Michael Tatzel </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 28th January 1992	Date of Mailing of this International Search Report <div style="text-align: center; font-size: large;">12 FEB 1992</div>	International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;">  Michael Tatzel </div>								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A2, 0350030 (CESKOSLOVENSKA AKADEMIE VED) 10 January 1990, see the whole document --	1-16
A	EP, A2, 0370827 (VISTAKON, INC.) 30 May 1990, see the whole document -- -----	1-16

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01887

SA 52703

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 31/10/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4038264	26/07/77	AT-B- 333033	25/10/76
		AT-B- 342335	28/03/78
		AU-D- 7703374	01/07/76
		BE-A- 824162	02/05/75
		CA-A- 1034698	11/07/78
		DE-A- 2500403	17/07/75
		FR-A-B- 2256931	01/08/75
		GB-A- 1496062	21/12/77
		JP-C- 1214162	27/06/84
		JP-A- 50107946	25/08/75
		JP-B- 58045688	12/10/83
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		DE-C- 2954547	13/10/88
		FR-A-B- 2417782	14/09/79
		GB-A-B- 2014591	30/08/79
		JP-C- 1599527	31/01/91
		JP-B- 2019925	07/05/90
		JP-A- 2147613	06/06/90
		JP-B- 3040060	17/06/91
		JP-A- 54118455	13/09/79
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EP-A2- 0350030	10/01/90	JP-A- 2073812	13/03/90
		US-A- 4916197	10/04/90
EP-A2- 0370827	30/05/90	AU-D- 4555089	31/05/90
		CA-A- 2003806	25/05/90
		CN-A- 1045270	12/09/90
		JP-A- 2219831	03/09/90
		US-A- 4889664	26/12/89
		US-A- 5039459	13/08/91

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

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